Remarks:

Claims 1-9, 12, 13 and 16-25 are pending.

No new matter is introduced by way of this amendment and entry thereof is respectfully requested.

I. Rejections under 35 U.S.C. §102(b)

Claims 1-4, 6-9 and 16-18 are rejected under 35 U.S.C. §102(b) as being anticipated by Cohn (US Patent 4,868,179) with evidence provided by Hunter et al (US 5,716,981).

Applicants respectfully traverse this rejection.

The claims as pending are directed to sustained release oral formulations comprising biodegradable microparticles and/or nanoparticles having dispersed therein a therapeutically effective amount of at least one antioxidant and at least one of isosorbide dinitrate and isosorbide mononitrate, wherein the isosorbide dinitrate is present in an amount of about 30 milligrams per day to about 160 milligrams per day.

Cohn is cited by the Examiner for teaching a composition comprising hydralazine hydrochloride and isosorbide dinitrate within the dosage range of claim 1. However, Cohn's composition is not a sustained release formulation comprising biodegradable microparticles and/or nanoparticles having at least one antioxidant and at least one of isosorbide dinitrate and isosorbide mononitrate dispersed therein. As noted by the Examiner on page 4 of the Office Action "Cohn does not elaborate on a biodegradable micro- or nanoparticle sustained released pharmaceutical composition and further a composition comprising an isosorbide mononitrate, or a composition comprising ACE-inhibitor and isosorbide dinitrate".

Hunter is not analogous art as Hunter does not disclose **oral** (emphasis added) sustained release formulation comprising biodegradable microparticles and/or nanoparticles having dispersed therein a therapeutically effective amount of at least one antioxidant and at least one of isosorbide dinitrate and isosorbide mononitrate. Hunter discloses formulations that are delivered directly in to the blood vessel, (see for example, Column 4, lines 14 to 20) tumor excision sites (see, Column 4, lines 42 to 47); cornea (see Column 4, lines 48 to 53) or joints (see Column 5, lines 28 to 33). Additionally Hunter discloses medical devises such as stents that are inserted directly into a passage way (see Column 4, lines 21 to 41; Column 5, lines 1 to 16).

Neither Cohn nor Hunter discloses the oral sustained release formulation comprising biodegradable microparticles and/or nanoparticles having dispersed therein at least one antioxidant and at least one of isosorbide dinitrate and isosorbide mononitrate. The formulations of the invention are not disclosed in either Cohn or Hunter and are different from the formulations described in Cohn or Hunter, and there is no motivation for one skilled in the art to make the claimed oral formulations based on the teachings in Cohn or Hunter.

Applicants respectfully submit that Cohn with evidence provided by Hunter does not anticipate the pending claims and withdrawal of this rejection is respectfully requested.

II. Rejection under 35 U.S.C. §103

Claims 1-4, 6-9, 12-13 and 16-25 are rejected under 35 U.S.C. §103 as being unpatentable over Cohn (U. S. Patent No. 4,868,179) in view of Hunter (U.S. Patent 5,716,981) and Klemsdal (Eur. J. Clin. Pharmacol. 1994), Wikipedia, and Chobanian et al (U. S. Patent No. 5,645,839).

Applicants respectfully traverse the rejection and respectfully submit that the claimed invention is unobvious over the cited references and there is no motivation to combine the cited references to arrive at the presently claimed invention. Applicants respectfully submit that the cited references, individually or in combination, do not disclose or suggest, or provide motivation to arrive at the presently claimed invention.

The pending claims are directed to sustained release oral formulations comprising biodegradable microparticles and/or nanoparticles having dispersed therein a therapeutically effective amount of at least one antioxidant and at least one of isosorbide dinitrate and isosorbide mononitrate, wherein the isosorbide dinitrate is present in an amount of about 30 milligrams per day to about 160 milligrams per day.

As noted previously, Cohn's composition is not a sustained release oral formulation comprising biodegradable microparticles and/or nanoparticles having at least one antioxidant and at least one of isosorbide dinitrate and isosorbide mononitrate dispersed therein. The specification defines "sustained release" on page 5, line 31 to page 6, line 3 as the release of a therapeutically active compound such that blood levels of the therapeutically active compound are within a desirable therapeutic range over an extended period of time. As further described in

the specification on page 33, line 10 to page 34, line 17, sustained release formulations of the invention can be achieved by encapsulating the therapeutic agents in biodegradable dosage forms such as microparticles, nanoparticles, and the like, wherein the therapeutic agents are dispersed within the dosage form. Biodegradation of the dosage form over time releases the therapeutic agents for cellular uptake. Additionally as mentioned above, the Examiner on page 4 of the Office Action admits that "Cohn does not elaborate on a biodegradable micro- or nanoparticle sustained released pharmaceutical composition and further a composition comprising an isosorbide mononitrate, or a composition comprising ACE-inhibitor and isosorbide dinitrate".

Applicants submit that nowhere in the teachings of Cohn is there any suggestion or motivation to make sustained release formulations comprising biodegradable microparticles and/or nanoparticles having dispersed therein a therapeutically effective amount of at least one antioxidant and at least one of isosorbide dinitrate and isosorbide mononitrate.

Hunter disclosed anti-angiogenic compositions comprising a wide variety of compounds. As discussed above Hunter's composition are not **oral** formulations comprising an antioxidant, such as, a hydralazine compound, and at least one of isosorbide dinitrate and isosorbide mononitrate. In fact Hunter does not disclose or suggest **oral** formulations. Applicants submit that nowhere in the teachings of Hunter is there any suggestion or motivation to make oral formulations comprising an antioxidant, such as a hydralazine compound, and at least one of isosorbide dinitrate and isosorbide mononitrate. Additionally the role of the antioxidant in Hunter's formulations is as a pharmaceutically or physiologically acceptable carrier, excipient or diluent (see Column 37, lines 50 to 63)

Klemsdal and the Wikipedia entry are cited by the Examiner for teaching the similar effect of administering either isosorbide dinitrate or isosorbide mononitrate. However, neither Klemsdal nor Wikipedia cures the deficiencies of Cohn in view of Hunter, as neither reference teaches or suggests sustained release oral formulations comprising biodegradable microparticles and/or nanoparticles having at least one antioxidant and at least one of isosorbide dinitrate and isosorbide mononitrate dispersed therein.

Chobanian is cited by the Examiner for teaching a composition comprising an ACE inhibitor, a nitric oxide stimulator and at least one pharmaceutically acceptable carrier. However, Chobanian does not cure the deficiencies of Cohn in view of Hunter, as Chobanian does not teach or suggest sustained release oral formulations comprising biodegradable

microparticles and/or nanoparticles having at least one antioxidant and at least one of isosorbide dinitrate and isosorbide mononitrate dispersed therein

In view of the above, Applicants submit that the claims are patentable over the combination of Cohn, Hunter, Klemsdal, Wikipedia, and Chobanian. Withdrawal of this rejection is respectfully requested.

IV. Conclusion

In view of the above, Applicants believe the pending application is in condition for allowance.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 08-0219, under Order No. 0102258.00170US2 from which the undersigned is authorized to draw.

Respectfully submitted,

Dated: July 11, 2008

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